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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/738,423
Filing Date: December 16, 2003
Appellant(s): KING ET AL.

Albert Wai-Kit Chan

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed October 9, 2008 appealing from the Office action mailed December 20, 2007.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Low *et al.* Nat Biotech 1999;17:37-41.

Schachter *et al.* Cancer Biother Radiopharm 1998 Jun;13:155-64.

Pawelek *et al.* Cancer Res 1997;57:4537-44.

Jirillo *et al.* Int J Immunopharmacol 1986;8:881-6.

(9) Grounds of Rejection

As an initial matter, the elected invention for examination in this application is drawn to a method of inhibiting cancer using a combination of an anti-cancer compound and attenuated tumor-targeted bacteria, and species election drawn to the combination of bacteria *Salmonella* and cisplatin. During prosecution, the claims have been narrowed to a mutant strain of *Salmonella* i.e. msbB$^-$. The claims have been examined to the extent that read on the elected invention.

The following ground(s) of rejection are applicable to the appealed claims:

Claim Objections

Claim 122 is objected to because it is a duplicate of claim 121.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 113, 116, 117, 119, 120, 123, 124 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Low et al.* (Nat Biotech 1999;17:37-41, IDS), in view of *Schachter et al.* (Cancer Biother Radiopharm 1998 Jun;13:155-64).

Low et al. teaches a method of inhibiting tumor growth comprising administering msbB$^-$ mutant *Salmonella* bacteria to mice having solid melanoma, which resulted in reduced tumor volume in the treated group compared to untreated controls (e.g. figs. 4, 5). *Low et al.* teaches the msbB$^-$ mutant *Salmonella* contain a disruption in the msbB gene which reduces TNF-α induction (attenuated) but retains its tumor-targeting property (tumor-targeted), i.e. exhibiting tumor accumulation ratios in excess of 1000:1 compared to its distribution in normal tissues (e.g. the abstract). *Low et al.* conducted tests in mice, swine, human monocytes and mouse macrophages, and concluded that [the results] "HAVE BEEN CONSISTENT WITH THE NOTION THAT THE MSBB- BACTERIA CAN BE SAFE

FOR USE IN HUMANS" (2nd paragraph, page 40). The teaching of *Low et al.* differs from instant claims in that it does not explicitly teach combining the bacteria therapeutic regimen with a chemotherapeutic agent such as cisplatin.

Schachter et al. supplemented *Low et al.* by disclosing a combined biotherapy and multi-drug chemotherapy (comprising cisplatin, an anti-cancer compound) for treating human melanoma and establishing that at the time of priority date a combined drug therapy had been clinically routine because one single drug was often insufficient for combating cancer. *Schachter et al.* also supplemented *Low et al.* by illustrating it was known in the art to combine a routine chemotherapeutic regimen with a newly developed biotherapy in treating solid tumors such as melanoma. *Schachter et al.* presented a chemo-biotherapy protocol for patients with metastasis melanoma by including cytokines that regulate patients' immune system with the conventional multi-drug chemotherapy (e.g. table 2, page 157). *Schachter et al.* applied the biotherapy and chemotherapy sequentially, i.e. modulating a patient immune system before or after the chemotherapy.

The rationale for the design of the combined therapy taught by *Schachter et al.* was to achieve a higher rate of a complete response (CR, meaning disappearance of all measurable disease) to drug treatment, and hence has been used as one of the criteria for evaluation (e.g. *Schachter*, last paragraph page 157). *Schachter et al.* teaches that conventional chemotherapy such as a 4-drug regimen (BCNU, DTIC, **cisplatin** and tamoxifen) could have 40-50% response rate in patients being treated, but only 10-14% of patients achieved a complete response. When using the chemo-biotherapy, the

response rate was 50%, and the complete response rate was up to 22% (e.g. pages 159-160). Although *Schachter et al.* does not teach tumor-targeted bacteria specifically, the reference illustrated the need of further improvement of the conventional chemotherapy.

Moreover, in the cancer research art, animal studies for new means of treatment often use a single means approach to obtain a clear reading of the treatment effect. Subsequently when the new means being applied in humans, one often combines it with a conventional therapeutic regimen to ensure the control of cancer growth. In a clinical setting, the skilled rarely uses only one drug/one type of therapy in a cancer therapeutic regimen, particularly when the therapeutic approach is relative new to the field. The prior art is replete with combination therapies combining chemotherapy with radiotherapy or newly developed cytokine, bacteria, gene therapy, *Schachter et al.* was only one of many.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to apply newly developed therapeutic means in the art and combine such with a conventional anti-cancer drug regimen for safety and effectiveness, and hence it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the attenuated tumor-targeted mutant *Salmonella* therapy as taught by *Low et al.* with the cisplatin chemotherapeutic regimen as taught by *Schachter et al.* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention for maximal therapeutic effects. Given the state of the art that the conventional therapy alone was

often insufficient in combating cancer, given the skilled was constantly searching for new means to improve conventional cancer treatment, and given that each of the cited references teaches an agent that is effective in cancer therapy, one would have had a reasonable expectation of success when combining the two. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 115, 121, 122 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Low et al.* (Nat Biotech 1999;17:37-41, IDS), in view of *Schachter et al.* (Cancer Biother Radiopharm 1998 Jun;13:155-64) as applied to claims 113, 116, 117, 119, 120, 123, 124 above, further in view of *Pawelek et al.* (Cancer Res 1997;57:4537-44, IDS).

The claims are directed to specifically treating colon or lung cancer. *Low et al.* in view of *Schachter et al.* illustrated the tumor-suppressing effect of attenuated *Salmonella* on melanoma, not particularly lung or colon cancer.

Pawelek et al. supplemented the teaching by establishing it was well known in the art that the attenuated *Salmonella* is capable of targeting multiple tumors including colon and lung carcinoma (e.g. paragraph bridging 4537-8, fig. 2), while it was well known in the art a chemotherapeutic compound such as cisplatin has been a commonly used compound for treating wide variety of solid tumors including lung and colon cancer.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the regimen as taught by *Low et al.* in view of

Schachter et al. for treating colon or lung cancer with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the lack of cure in cancer therapy in general, and the need for developing new therapeutic regimens for treating any type of cancer including colon and lung cancer. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

The appellant's arguments are addressed in the order they appeared.

1. The appellant argues, "the examiner's stated rationales fail to articulate grounds for a reasonable expectation of success or anticipated success".

In this section, the applicant cited KSR case law and two paragraphs of previous Office action deemed at addressing the appellant's previous arguments, one using *In re Kerkhoven* for analysis of obviousness when combining two known compositions each of which is taught by the prior art to be useful for the same purpose; and the other citing KSR for pointing out it is not necessary for the references to contain a specific teaching, suggestion or motivation to combine. The Office maintains the aforementioned standing and analysis.

The appellant then alleges "contained nowhere in the Examiner's rejections is there any rationale that results were 'predictable' beyond the conclusory allegation".

The argument has been fully considered but found not persuasive. This is because the rationale for a reasonable expectation of success has been consistently expressed in the rejection throughout the prosecution history, i.e. considering the outcome disclosed in each of the references when the two agents were used separately for treating the same type of cancer/tumor. The factual evidence speaks for themselves, and the articulation are reflected in the rejections *supra* and in the paragraphs cited by the appellant. In summary, the bacteria therapy has been proven effective in treating melanoma as taught by *Low et al.*, and the cisplatin has been proven effective in treating melanoma as shown by *Schachter et al*. It would have been *prima facie* obvious to one of ordinary skill in the art to combine these compositions to generate a new composition for the treatment of melanoma with a reasonable expectation of success. Note that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that are required is a reasonable expectation of success. See In re O'Farrell, 7 USPQ2d 1673 (CAFC 1988).

The appellant is reminded during the course of prosecution, the Office also cited the following case law analysis for articulation:

"AN EXPRESS SUGGESTION TO SUBSTITUTE ONE EQUIVALENT COMPONENT OR PROCESS FOR ANOTHER IS NOT NECESSARY TO RENDER SUCH SUBSTITUTION OBVIOUS". In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

"FINDING OF OBVIOUSNESS DOES NOT REQUIRE EXISTENCE OF EXPRESS, WRITTEN MOTIVATION TO COMBINE IN PRIOR ART, SINCE MOTIVATION TO COMBINE MAY BE FOUND IN NATURE OF

PROBLEM TO BE SOLVED, LEADING INVENTORS TO LOOK TO REFERENCES RELATING TO POSSIBLE SOLUTIONS TO THAT PROBLEM". (*Ruiz v. A.B. Chance Co.*, 69 USPQ2d 1686 CA FC 2004).

"FINDING OF MOTIVATION TO COMBINE PRIOR ART REFERENCES NEED NOT BE SUPPORTED BY SHOWING THAT CLAIMED COMBINATION IS *PREFERRED OVER OTHER ALTERNATIVES*, SINCE PROPER INQUIRY IS WHETHER THERE IS SOMETHING IN PRIOR ART AS WHOLE TO SUGGEST DESIRABILITY, AND THUS OBVIOUSNESS, OF MAKING COMBINATION, NOT WHETHER THERE IS SOMETHING IN PRIOR ART AS WHOLE TO SUGGEST THAT COMBINATION IS PREFERRED OR MOST DESIRABLE. (*In re Fulton*, 73 USPQ2d 1141 CA FC 2004).

Hence, even though *Schachter et al.* did not teach combining specifically the cisplatin and the attenuated *Salmonella*, both *Low et al.* and *Schachter et al.* teach new means of treating cancer, particularly melanoma, it would have been obvious to the skilled artisan to look for available new means in the art and combining such with conventional therapeutic means according to the nature of the problem to be solved, i.e. treating solid tumor cancer. Again, the instant situation is amenable to the type of analysis set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980), wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to produce a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Given the teaching of the prior art compositions of cisplatin and attenuated *Salmonella*-all taught to be useful for the treatment of melanoma, it would have been *prima facie* obvious to one of

ordinary skill in the art to combine these compositions to generate a new composition for the treatment of cancer with a reasonable expectation of success.

2. The appellant asserts "A person of Ordinary skill in the art would not have had a reasonable expectation of success with respect to the combination of Low and Schachter as of the date of invention".

The appellant argues it would have been particularly counterintuitive to combine a live Salmonella bacterium with a conventional chemotherapy at the time of invention give that bacterial infection was a well-known occurrence among immune-compromised cancer patients undergoing chemotherapeutic therapy.

The argument has been fully considered but found not persuasive. This is because almost each of chemotherapeutic compounds in cancer therapeutic regimen would weaken a patient's immune system individually, but weighing the pros and cons, the skilled artisan still combine multiple compounds for the need of combating hard to kill tumor cells, it is a matter of balancing the beneficial and damaging effects of an anti-cancer drug regimen. In the instant case, *Low et al.* clearly teaches that the mutant strain of *Salmonella* was attenuated by auxotrophic mutations that would limit their pathogenesis in normal tissues but retained the high-level replication in a tumor-selective manner following systemic administration (see the abstract and 1st paragraph, page 37). Apparently, *Low et al.* was aware of the potential hazard using *Salmonella* in cancer therapy, and attempting to minimize the toxic effect while utilizing its tumor-targeting effect. Further, as shown by *Schachter*, it was within the levels of the skilled to

determine the appropriate timing of drug administration in the combination therapy. For example, *Schachter et al.* did not use the biotherapy with the chemotherapy simultaneously, rather, they use such sequentially, i.e. modulating a patient immune system before or after the chemotherapy. Accordingly, it would have been within the knowledge of the skilled in the art to wisely use the newly developed bacteria therapy with a conventional chemotherapy sequentially to minimize side effects.

Further, considering that the biotherapy taught by *Schachter et al.* is for priming and immune regulation, there was evidence in the prior art showing that attenuated *Salmonella* also have priming and immune regulation effect. *Jirillo et al.* (Int J Immunopharmacol 1986;8:881-6) teaches that attenuated *Salmonella* bacteria enhance immune responsiveness in patients with gynecologic malignancies via immune regulation (see e.g. the abstract). Thus, attenuated *Salmonella* taught by *Low* has similar underlying principle as does the biotherapy taught by *Schachter* in treating cancer. Accordingly, it was not counterintuitive for the skilled to combine the bacteria therapy with the conventional therapy when used with caution.

3. The appellant alleges "the stated need in the field of endeavor is overbroad, the scope and content of the prior art is overbroad, and the obviousness rationale fails to evidence predictability".

In this section, the appellant first alleges that the examiner provides an extremely broad problem to be addressed citing the phrase used in the Office action dated

12/20/07, which is reiterated *supra* in the rejection "The rationale for the design of the combined therapy was to achieve a higher percentage of a complete response…".

The argument has been fully considered but found not persuasive because the phrase and paragraph was an analysis and summary of the results reported in *Schachter* on specific data presented, not a broad statement regarding the need in the field of endeavor in general.

The appellant then asserts, under the aforementioned rationale, nearly any combination of therapies might be considered obvious if each separately performed a stated function of decreasing measurable disease. In response, the Office did not try to reach a broad conclusion but making analysis based on the fact pattern of the cited particular prior art, and the knowledge of the skilled in the art. The claimed invention is not just any combination of therapies, but combining a conventional regimen with a new approach for treating the same type of diseases. Moreover, the *In re Kerkhoven* case law was a conclusion held by the court.

The appellant then attests that the devices of the prior art are not to be considered analogous because the biotherapy of Schachter is too different from a living replicating bacteria.

In response, the bacteria therapy has been proven effective in treating melanoma by *Low et al*, and the cisplatin has been proven effective in treating melanoma as shown by *Schachter et al*. They are apparently not entirely different fields of therapies. They both were proven effective options available in the art for treating melanoma. Moreover, considering that the biotherapy taught by *Schachter et al* is for priming and immune

regulation, there was evidence in the prior art showing that attenuated *Salmonella* also have priming and immune regulation effect. *Jirillo et al* (Int J Immunopharmacol 1986;8:881-6) teach that attenuated *Salmonella* bacteria enhance immune responsiveness in patients with gynecologic malignancies via immune regulation (see e.g. the abstract). Thus, attenuated *Salmonella* has similar underlying principle as does the biotherapy in treating cancer. The court has held "ARGUMENT THAT TWO REFERENCES ARE NONANALOGOUS IS WITHOUT MERIT WHERE BOTH ARE CONCERNED WITH IDENTICAL FIEDL OF ENDEAVOR". *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Hence, it would have been *prima facie* obvious to one of ordinary skill in the art to combine these therapeutic options to generate a new regimen for the treatment of cancer.

The appellant went on to argue that no incentives or market force are identified beyond the general goal of improving chemotherapy and eliminating disease states.

In response, improving chemotherapy and eliminating cancer is an extremely important motive or incentive for researchers and physicians alike to combine existing therapeutic options, and when such efforts were successful, it would eventually be a driving force of the market.

The appellant argued claims 123 and 124 separately but reiterated the same lines of arguments, which have been addressed *supra*.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Q. JANICE LI, M.D./

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